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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,875	08/21/2002	Pramod K. Srivastava	8449-086-999	2913

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EXAMINER	
SZPERKA, MICHAEL EDWARD	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 11/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,875	SRIVASTAVA ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-16,20-23,26-28 and 41-43* is/are pending in the application.

4a) Of the above claim(s) *27 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *5-16, 20-23, 26, and 41-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This application is the national stage entry of PCT/US00/2471, which is a continuation in part of USSN 09/393,652.

Applicant's response and amendments received August 5, 2005 are acknowledged.

Claims 1-4, 17-19, 24, 25, and 29-40 have been cancelled.

Claims 5, 7, 9, 14-16, 20-23, and 26 have been amended.

Claims 41-43 have been added.

Claims 27 and 28 stand withdrawn for the reasons of record set forth in the office action mailed April 7, 2005.

Claims 5-16, 20-23, 26-28, and 41-43 are pending in the instant application.

Claims 5-16, 20-23, 26, and 41-43 are under examination in this office action.

Priority

2. It is noted that USSN 09/393,652 has been revived and as such no amendment to the first line of the specification is currently required. Applicant is reminded to update the priority information in the first line of the specification if the status of USSN 09/393,652 changes.

Claim Objections

3. The claim objections of record concerning dependency of claims to claims in non-elected groups and for failure to further limit the claims have been overcome by either amending or canceling the objected claims.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-16, 20-23, and 26 stand rejected and new claims 41-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention for the reasons of record set forth in the office action mailed April 7, 2005.

Applicant's arguments filed August 8, 2005 have been fully considered but they are not persuasive. Applicant acknowledges that none of the working examples in the specification demonstrate the efficacy of heat shock proteins that are not complexed with peptides, and then argues that the specification is still enabling. Applicant bases this argument on an example in the specification wherein heat shock proteins isolated

from either liver or skin could inhibit the rejection of a skin graft. Because of this, applicant further argues that "the ability to inhibit a graft rejection is not dependent on the *identity* of the peptides complexed with the heat shock protein" (see particularly the lower third of page six of the response, emphasis added by the examiner). Based upon the data presented in the specification, the examiner concurs that the *identity* of the peptides complexed with the heat shock protein is not critical. What the examiner believes *is* critical is that the heat shock proteins *be* complexed with peptides, the identity of said peptides being non-critical. Support for this position is found in the teachings of Attfield (US Patent No. 5,891,653, of record), which states that heat shock proteins must be complexed with peptides in order to retain their biological activity with regard to the modulation of the immune response (see entire document, particularly lines 42-47 of column 4). Applicant has criticized the teachings of Attfield, and the examiner's reliance on them, by arguing that the statement by Attfield concerning the maintenance of biological activity of heat shock proteins is unsubstantiated by any data or other evidence provided by Attfield (see particularly the penultimate sentence of page 6 of the reply). The examiner is confused as to why applicant believes that the statement of Attfield is unsubstantiated and why applicant apparently believes that the removal of peptides from heat shock proteins does not cause a loss of biological activity. In the paragraph that spans pages 7 and 8 of the response, applicant indicates numerous assays to determine if a heat shock protein is "substantially free" of peptides, with many of these assays relying on measuring the biological activity of the heat shock protein using cytotoxic T lymphocytes. Indeed, applicant states in the last sentence of

the paragraph that spans pages 7 and 8 of the reply "One of skill in the art would regard as "substantially free" of complexed antigenic molecule a heat shock protein preparation that failed to produce a biological response in such an assay for antigenicity or immunogenicity." As such, it appears that applicant is indicating that removal of complexed peptides from heat shock proteins results in the loss of the biological activity of the heat shock protein, in accord with the teachings of Attfield. Therefore, the rejection of record has been maintained.

Note that new claims 41-43 have been added to this rejection. These claims limit the claimed invention to human gp96, hsp70, and hsp90. Previously rejected claims recited mammalian gp96, hsp70 and hsp90, and since humans are members of the genus of mammals, inclusion of these new claims with the rejection of record is appropriate.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5-16, 20-23, and 26 stand rejected and new claims 41-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention due to the recitation of the limitation "substantially free" for the reasons of record set forth in the office action mailed April 7, 2005.

Applicant's arguments filed August 8, 2005 have been fully considered but they are not persuasive. Applicant argues that methods were well know in the art at the time

the invention was filed to determine if heat shock proteins did or did not contain complexed peptides, and has cited multiple pieces of art to support this position. The examiner agrees that a skilled artisan could ascertain if a heat shock protein was or was not free of bound peptides at the time the application was filed. However, it is still not clear to the examiner what "substantially free" means. The arguments and art teachings presented in the paragraph that spans pages 7 and 8 of the reply all indicate methods that determine if peptides are or are not complexed with heat shock proteins. The definition of "substantially free" based upon the biological activity of heat shock proteins appears to be directly dependent upon the presence of peptides bound to the heat shock proteins, with heat shock proteins without peptides yielding no biological response and heat shock proteins with peptides yielding a measurable biological response. If no biological response is obtained it appears reasonable, based on applicant's arguments and the prior art contained therein, to say that the heat shock protein is free of peptides. What else can be present with a heat shock protein such that it does not yield a biological response yet is only "substantially free" of peptides? Appropriate clarification of the claims is still required.

Note that new claims 41-43 have been added to this rejection. These claims limit the claimed invention to human gp96, hsp70, and hsp90. Previously rejected claims recited mammalian gp96, hsp70 and hsp90, and since humans are members of the genus of mammals, inclusion of these new claims with the rejection of record is appropriate.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 5-10, 12, 14, 16, 20-22, and 26 stand rejected and new claim 42 is rejected under 35 U.S.C. 102(b) as being anticipated by Berberian et al., US Patent No. 5,348,945, of record as reference A02 on the IDS filed 1/13/05, see entire document) for the reasons of record set forth in the office action mailed April 7, 2005.

Applicant's arguments filed August 8, 2005 have been fully considered but they are not persuasive. Specifically, applicant argues that the teachings of Berberian et al. do not anticipate the claimed invention because Berberian et al. do not teach treating graft rejection in a mammal by administering a heat shock protein to a mammal. The examiner respectfully disagrees.

As was indicated by applicant on pages 8 and 9 of the reply filed August 5, 2005, Berberian et al. do teach the administration of hsp70 *in vivo*. The administration of hsp70, which may occur *in vivo* or *in vitro*, is taught as enhancing the survival of cells residing in tissue (see particularly lines 31-34 of column 2 of Berberian et al.). While applicant is correct in stating that Berberian et al. teach the treatment of tissues ex vivo prior to transplantation, applicant's attention should be drawn to lines 1-8 of column 3, wherein Berberian also teach that "tissues of any origin, including animal and plant tissue, may be treated by the method of the present invention either *in vitro* or *in vivo*."

As such, Berberian et al. do teach the administration of heat shock proteins in vivo to a mammal in a transplantation setting. While it is true that Berberian et al. do not specifically teach that the administration of hsp70 inhibits graft rejection, the do clearly teach that such treatment enhances the survival of cells. During rejection of a graft, the immune system of the graft recipient mounts an immune response that attacks the cells of the graft. As such, the survival of the cells of the graft is compromised. Berberian et al. teach that administering hsp70 enhances the survival of cells, and an enhancement of the survival of the graft cells indicates that the process of graft rejection has been inhibited. Therefore, the rejection of record has been maintained.

It should be noted that new claim 42 has been added to this rejection. Claim 42 teaches that the administered heat shock protein is human hsp70. Berberian et al. teach that the hsp70 to be used in performing their disclosed methods can be of mammalian origin, and they further disclose that humans are encompassed by the use of the term mammalian in their specification (see particularly lines 1-8 of column 3 and lines 17-33 of column 5). As such, the teachings of Berberian et al. teach this newly introduced limitation and therefore claim 41 has been properly added to this rejection.

Double Patenting

8. Claims 5-7, 9-16, 20-23, and 26 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 22 of U.S. Patent No. 6,007,821. Although the conflicting claims are not identical, they are

not patentably distinct from each other because they anticipate the claimed invention for the reasons of record set forth in the office action mailed April 7, 2005.

Applicant's arguments filed August 8, 2005 have been fully considered but they are not persuasive. Applicant's first line of argument is that the patented claims do not anticipate the instant claims because treating an autoimmune disease and treating rejection of a grafted cell, tissue or organ are different clinical entities. While transplant rejection and autoimmune diseases are broadly separable, there is some overlap between the two conditions. Specifically, the '821 patent teaches a preferred embodiment wherein gp96 is administered to diabetic patients undergoing islet cell transplantation. This is done because the grafted islet cells of transplant recipients are prone to the same autoreactive damage that originally destroyed the host cells (see particularly lines 20-24 of column 27 of '821). As such, the autoimmune disease is responsible for rejecting (destroying) the grafted islet cells. As such, performing the method of claim 22 in diabetic patients undergoing islet cell transplantation would anticipate the instant claimed methods.

Applicant's second line of arguments is that that practicing claim 22 of the '821 patent would not treat rejection of the transplant recited in patented claim 22 because (1) not every transplant is rejected and (2) patented claim 22 does not specify when the heat shock protein is administered. It is true that not all transplants will be rejected. However, some will be rejected, and those that are rejected, such as in the preferred embodiment of treating islet cell transplantation, anticipate the claimed methods. Further, applicant's arguments about the timing of heat shock protein administration are

not relevant since the timing of the administration is not specified in either the patented claims or the instant claims. It should be noted that applicant's arguments concerning the inefficacy of administration prior to transplantation are misleading based upon the working examples provided in experiments 1 and 2 of the instant specification (see particularly pages 39-42). In these examples, heat shock proteins are administered prior to transplantation, with said administration resulting in an inhibition of graft rejection. As such, administration before graft rejection becomes clinically apparent does work, but it is not clear from the instant specification that administration of heat shock proteins subsequent to clinical symptoms of graft rejection inhibits an active graft rejection reaction. However, since the timing of administration is not a limitation of the claims, arguments concerning differences in the timing of heat shock protein administration are not relevant.

Applicant has also argued that the indication that claims 4, 9, 11, 31 and 39 of the '821 patent also anticipate the instant invention is improper because these claims do not recite a transplant, and thus cannot anticipate the instant invention. Upon further review, the examiner agrees that these patented claims do not directly anticipate the claimed invention. As explained above, patented claim 22 does anticipate the claimed invention and therefore this rejection has been maintained.

9. No claims are allowable.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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March 28, 2005

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